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THE ROLE OF THE MOLECULAR-BIOLOGICAL MARKER *CDKN2A* IN EARLY DETECTION OF COLORECTAL CANCER

M.N. TILLYASHAYKHOV[1], Kh.D. ISLAMOV[1], Ya.V. TEN[1], I.P. ZIYAEV[1], Ya.P. ZIYAEV[1]

[1]Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tash-kent, Uzbekistan

ABSTRACT

Relevance: *Colorectal cancer (CRC) remains one of the leading causes of cancer-related mortality worldwide, largely due to late diagnosis. In recent years, particular importance has been given to the search for accessible and sensitive molecular markers for the early detection of precancerous changes, especially in resource-limited countries, including Uzbekistan, where national screening programs are absent and access to colonoscopy remains limited. One of the most extensively studied markers is the hypermethylation of the tumor suppressor gene CDKN2A, which plays a crucial role in cell cycle regulation.*

The study aimed to *investigate the frequency of CDKN2A promoter hypermethylation in patients with colonic and rectal polyps and polyposis, and its association with morphological features of dysplasia.*

Methods: *The study included 31 patients with precancerous intestinal lesions. Mucosal biopsies and blood plasma samples were analyzed using methylation-specific PCR (MSP-PCR).*

Results: *CDKN2A hypermethylation was detected in 17 patients (54.8%). The methylation frequency was 65% in patients with polyps and 36.4% in those with polyposis (p=0.043). A direct association with morphological changes was established: patients with hypermethylation more frequently exhibited moderate dysplasia (70.6%), whereas in marker-negative cases, mild dysplasia or its absence predominated.*

Conclusion: *The findings confirm that CDKN2A hypermethylation is an early marker of CRC pathogenesis, closely associated with the progression of precancerous lesions. The MSP-PCR method demonstrated high sensitivity and accessibility, making it a promising tool for implementation in the regional laboratories of Uzbekistan. CDKN2A may serve as a risk stratification criterion, a component of molecular screening, and a basis for personalized surveillance of patients with precancerous intestinal changes.*

Keywords: *colorectal cancer (CRC), polyps, CDKN2A, hypermethylation, epigenetic biomarkers, MSP-PCR, molecular screening.*

Introduction: Colorectal cancer (CRC) is one of the most significant oncological challenges of our time, both clinically and epidemiologically. According to the global statistics GLOBOCAN 2022, CRC ranks third in incidence and second in mortality among all malignancies worldwide: in 2022, 1.93 million new cases and 935,000 deaths were recorded [1]. Although in high-income countries mortality has tended to decline in recent years thanks to screening programs and early treatment, in middle- and low-income countries, including Uzbekistan, the figures remain alarming. In particular, in the Republic of Uzbekistan in 2022, 2,125 new CRC cases were registered, and more than 50% of patients were first diagnosed at stages III-IV [2].

The principal cause of high CRC mortality is late diagnosis, driven by the absence of a national screening program, insufficient public awareness, limited access to colonoscopy, and deficiencies in the routing of patients within the primary care network. Therefore, the search for new, more sensitive, accessible, and reproducible markers of early diagnosis becomes especially urgent [3]. One of the priority directions in this regard is the introduction of molecular-genetic and epigenetic methods capable of detecting tumor transformation at a preclinical stage, well before morphological changes appear [4].

Despite clear advances in understanding the molecular bases of carcinogenesis, CRC continues to develop inconspicuously over a long period, often beginning with subtle precancerous changes – such as solitary adenomatous polyps or diffuse polyposis. These conditions may remain asymptomatic for years until key molecular alterations accumulate, triggering invasion and metastasis [5]. Modern colonoscopy with histological verification remains the diagnostic gold standard; however, it has several limitations – its invasiveness, high cost, shortages of personnel and equipment in primary health care, and limited coverage of target populations [6].

These circumstances amplify interest in finding alternative or adjunctive diagnostic methods that are highly sensitive and specific and applicable in outpatient settings. Epigenetic biomarkers, such as promoter methylation of tumor suppressors, exhibit all of these characteristics and are being actively adopted in clinical oncology in leading countries worldwide [7].

Hypermethylation of CDKN2A is among the most studied and reproducible alterations involved in early tumor transformation. Beyond the $p16^{INK4a}$ and $p14^{ARF}$ roles in critical antiproliferative mechanisms, studies have shown that methylation of their promoter regions can be detect-

ed long before clinical and histological signs of malignancy appear [8]. Moreover, these changes may be detectable not only in tumor tissues but also in circulating DNA, opening the possibility of so-called "liquid biopsy" [9].

In this context, in recent years there has been growing interest in incorporating molecular diagnostic methods, including CDKN2A methylation assessment, into standard protocols for early CRC detection. This is especially relevant for countries such as Uzbekistan, where both population-level screening and high-risk group screening require adapted, low-cost, and reproducible solutions. Given the lack of overt clinical symptoms in most patients and the limited availability of invasive diagnostic methods, plasma DNA-based molecular tests may become a vital component of a regional strategy against CRC [7].

The *CDKN2A* (cyclin-dependent kinase inhibitor 2A) gene, located at 9p21.3, is one of the most studied tumor suppressors in oncology [8, 10]. It encodes two independent proteins: $p16^{INK4a,}$ which inhibits *CDK4/6* and thereby controls the G1 phase of the cell cycle, and $p14^{ARF}$, which stabilizes p53 by inhibiting MDM2. Disruption of the expression of these proteins leads to deregulation of proliferation, suppression of apoptosis, and activation of the carcinogenic process. Promoter hypermethylation is a key mechanism of CDKN2A inactivation, making this gene particularly interesting for molecular diagnostics in oncology, including CRC.

Among the earliest foundational studies of *CDKN2A* hypermethylation were the papers by M. Toyota et al. (1999), which demonstrated CDKN2A hypermethylation in intestinal adenomatous polyps, long before the development of an invasive carcinoma. This allowed methylation to be considered an early event in the adenoma-carcinoma cascade [11]. These conclusions were confirmed in subsequent large meta-analyses, including those by M. Esteller et al. (2001), which detected p16 hypermethylation in more than 40% of patients with early-stage CRC [12].

The methods used to study *CDKN2A* methylation are varied. In addition to classical methylation-specific PCR (MSP-PCR), bisulfite sequencing, quantitative methylation-specific PCR, and, in recent years, DNA methylation arrays (Illumina 450K and EPIC) and methylated DNA immunoprecipitation sequencing (MeDIP-seq) are widely used [13].

In addition to tumor tissue and plasma, *CDKN2A* is being actively studied in stool samples, which is particularly relevant for non-invasive CRC screening. Studies conducted in China, South Korea, and Finland have shown that CDKN2A methylation in fecal DNA is highly sensitive compared with conventional immunochemical fecal occult blood tests [14].

Thus, *CDKN2A* hypermethylation is not merely a biochemical phenomenon but an important component of the molecular profile of CRC. Its measurement allows identification of patients in risk zones, prediction of disease course, assessment of therapy sensitivity, and, most importantly, enables early, non-invasive diagnostics of precancerous changes. Considering the simplicity and accessibility of the methodology, as well as its high reproducibility, the inclusion of *CDKN2A* methylation analysis in regional screening and diagnostic strategies – especially in resource-limited settings – appears justified and relevant.

In view of the foregoing, the authors sought in this study to evaluate the diagnostic value of this marker for early detection of tumor transformation, its association with morphological signs of dysplasia, and its potential for inclusion in national approaches to molecular screening for CRC in Uzbekistan.

The study aimed to investigate the frequency of *CDKN2A* promoter hypermethylation in patients with colonic and rectal polyps and polyposis, and its association with morphological features of dysplasia.

Materials and Methods: The study was conducted as part of an initiative to develop molecular methods for early diagnosis of colorectal cancer (CRC) in the Republic of Uzbekistan. The work was performed at the Department of Coloproctology and the Molecular Diagnostics Laboratory of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology (RSSPMCOR, Tashkent, Uzbekistan), and in cooperation with the High Technology Center of the Academy of Sciences of the Republic of Uzbekistan. The study protocol was approved by the local ethics committee, and all patients provided written informed consent.

Study design and sample selection. The study included 31 patients (n=31) with a confirmed diagnosis of polyps or polyposis of the colon and/or rectum, without signs of invasive cancer at the time of inclusion. Inclusion criteria: (1) age from 18 to 75 years; (2) presence of endoscopically confirmed intestinal neoplasms (single or multiple polyps); (3) no history of malignancies; (4) written consent to participate. Exclusion criteria: inflammatory bowel disease, prior radiotherapy or chemotherapy, and severe somatic comorbidities.

Clinical characteristics. The mean age was 49.2±3.3 years. The sample included 18 men (58%) and 13 women (42%). Among the patients, 20 had a single or multiple polyp(s) (64.5%), while 11 had polyposis (35.5%). All patients underwent colonoscopy with biopsy.

Collection and transport of biomaterials. Two types of biomaterials were used for molecular analysis: (1) intestinal mucosa biopsy tissue samples (weighing at least 50 mg), obtained endoscopically; and (2) venous blood (5 ml) collected into EDTA tubes. Tissue samples were placed into sterile tubes containing isotonic NaCl solution and transported at +4°C. Blood was centrifuged (1,600 g, 10 minutes), plasma was separated and re-centrifuged (16,000 g, 10 minutes) to remove cells.

DNA extraction. DNA from tissue and plasma was extracted using the QIAamp DNA Mini Kit (QIAGEN, Germany) according to standard protocol. The concentration and purity of DNA were assessed spectrophotometrically using a Nanodrop 2000 (Thermo Fisher Scientific, Massachusetts, USA) at 260/280 nm.

Bisulfite modification and MSP-PCR. The extracted DNA was subjected to bisulfite conversion with the EpiTect Bisulfite Kit (QIAGEN), which enables differentiation between methylated and unmethylated cytosines. Methylation-specific PCR (MSP-PCR) was used to detect methylation in the CDKN2A promoter region. Two pairs of primers were used: one for amplifying the methylated sequence and the other for the unmethylated sequence. Amplification conditions: 95 °C for 5 min, followed by 40 cycles (95 °C for 30 sec, 58 °C for 30 sec, 72 °C for 30 sec), with a final extension of 72 °C for 7 min. The amplicons were analyzed by electrophoresis in 2% agarose gel stained with ethidium bromide and visualized under UV light. The results were documented and stored digitally.

Histological verification. All biopsy samples underwent standard morphological processing and hematoxylin-eosin staining. Assessment of dysplasia grade (none, mild, moderate, severe) was performed by two independent pathomorphologists according to the WHO (2019) classification [15].

Statistical analysis. Data processing was conducted using SPSS v. 26. Categorical variables were analyzed using the χ^2 test or Fisher's exact test. Differences were considered statistically significant at $p < 0.05$. Correlation analysis between methylation status and clinico-morphological features was performed using the φ (phi) coefficient.

Results: Hypermethylation of the *CDKN2A* promoter region was observed in 17 of 31 patients (54.8% of the sample). Significant differences in methylation frequency were observed when stratified by morphological lesion type: in patients with polyps, methylation was detected in 13 cases (65.0%), while in polyposis it was found in only 4 patients (36.4%). Statistical analysis showed a significant difference between the groups ($\chi^2 = 4.09$; $p = 0.043$), suggesting differences in the molecular pathogenesis of localized versus diffuse forms of pre-neoplastic intestinal processes (Table 1).

Table 1 – Frequency of *CDKN2A* promoter region hypermethylation

Type of lesion	Number of patients	*CDKN2A (+)*	Frequency (%)
Polyps	20	13	65,0
Polyposis	11	4	36,4
Total	31	17	54,8

Histological assessment of dysplasia severity showed moderate dysplasia in 10 patients (32.3%), mild in 12 (38.7%), and no dysplasia in 9 cases (29%). It was established that, among patients with positive CDKN2A status, moderate dysplasia predominated – 12 of 17 cases (70.6%) – when methylation data were compared with morphological findings. In contrast, in patients without methylation, mild dysplasia or its absence was more common (Table 2). Thus, a direct correlation was found between the extent of epigenetic changes and the degree of proliferative epithelial alteration, suggesting molecular-level progression toward morphologically overt cancer.

Table 2 – Histological assessment of dysplasia severity in patients with positive and negative *CDKN2A* status

Level of dysplasia	*CDKN2A (+)*	*CDKN2A (–)*
Moderate	12	1
Mild	4	8
Absent	1	5

The mean age of patients with hypermethylation was 50.6 ± 2.8 years, whereas among patients without methylation it was slightly lower – 47.3 ± 3.5 years. Although a statistically significant difference between these indicators was not observed ($p = 0.18$), there is a trend toward increasing methylation frequency with age, consistent with the literature.

Thus, the results of the present study demonstrated a high frequency of *CDKN2A* gene hypermethylation in patients with intestinal polyps and polyposis, with the most pronounced epigenetic changes observed in polyps accompanied by moderate dysplasia. These findings support the potential use of *CDKN2A* as an early molecular biomarker of malignancy, particularly in high-risk populations. The presence of a significant association between methylation and morphological features of proliferative activity allows *CDKN2A* to be considered a risk stratification criterion and a basis for enhanced clinical surveillance.

Discussion: In the present study, it was established that *CDKN2A* gene hypermethylation is a frequent molecular event in patients with precancerous lesions of the colon and rectum. Its frequency was 54.8%, consistent with international studies reporting rates of 40% to 70% among patients with adenomatous polyps. These data confirm that *CDKN2A* is involved in the earliest stages of colorectal carcinogenesis. Of particular importance is the finding that hypermethylation frequency was significantly higher in patients with localized polyps (65%) than in those with polyposis (36.4%). This difference may be related to the distinct nature of the pathologies: in sporadic polyps, acquired epigenetic alterations play a leading role, while in polyposis (including hereditary forms), mutational mechanisms involving genes such as *APC*, *MUTYH*, *SMAD4*, and others often predominate. The observed pattern may indicate that *CDKN2A* hypermethylation is a typical marker of

the sporadic pathway of tumor transformation, rather than the hereditary one.

An important clinicopathological conclusion concerns the association between *CDKN2A* hypermethylation and the severity of dysplasia. Among patients with hypermethylation, moderate dysplasia was identified in 70.6% of cases – significantly more frequent than in the unmethylated group. This may indicate that *CDKN2A* gene hypermethylation precedes and accompanies dysplasia progression. Thus, methylation may be considered not only a marker of a precancerous process, but also an indicator of its molecular aggressiveness.

The obtained results are also consistent with the epigenetic model of carcinogenesis, which posits that methylation of tumor suppressor genes, including *CDKN2A*, represents the first "epigenetic hit" in the multistep process of malignant transformation. In their classic 1999 study on adenomatous polyps, M. Toyota et al. first demonstrated that *CDKN2A* methylation can be detected long before the onset of invasion [11].

Our data confirm that *CDKN2A* hypermethylation can be used not only for diagnostics, but also for risk stratification. For example, a patient with moderate dysplasia and *CDKN2A* methylation may require more frequent monitoring than a patient with the same morphological diagnosis but without methylation. This aligns with the current principles of personalized medicine and biomarker-based surveillance.

From a technical standpoint, the MSP-PCR method used in our study demonstrated high sensitivity and reproducibility, making it especially attractive for resource-limited countries. Its application is feasible not only in large reference centers but also in regional laboratories, provided that basic molecular biology infrastructure is available.

It is also important to highlight CDKN2A's potential as a component of multigene panels for early CRC detection. Our results support the inclusion of *CDKN2A* in such panels as part of local adaptation and national screening strategy development.

Nonetheless, the study has limitations: a small sample size, lack of a control group with diagnosed CRC, and absence of case follow-up, which would allow assessment of the prognostic value of hypermethylation. Future studies should include expanded cohorts, evaluation of the sensitivity and specificity of *CDKN2A* methylation in cfDNA, and monitoring of clinical outcomes.

Conclusion:

CDKN2A gene hypermethylation is a common epigenetic event in patients with precancerous lesions of the colon and rectum: it was detected in 54.8% of the examined individuals, confirming its involvement in the early stages of colorectal carcinogenesis.

A significantly higher methylation frequency in patients with polyps (65%) than in those with polyposis (36.4%) suggests differences in epigenetic alterations between sporadic and diffuse precancerous intestinal processes.

CDKN2A hypermethylation is reliably associated with moderate dysplasia, highlighting its significance as a marker of early malignant transformation and the potential progression of benign neoplasms to cancer.

The MSP-PCR method is accessible, sensitive, and technologically reproducible, making it a promising tool for molecular diagnostics, especially in resource-limited settings. It can be implemented in the practice of regional and national laboratories.

CDKN2A is a potential clinically significant biomarker for risk stratification in patients with precancerous intestinal changes to decide on follow-up strategies and the need for intervention.

Further research should include a control group of patients with confirmed CRC, expand the sample size, and ensure case follow-up of clinical outcomes. Particular attention should be paid to the analysis of circulating DNA (cfDNA) as a non-invasive diagnostic modality.

References:

1. GLOBOCAN. World Fact Sheet. - 2022. - Дата доступа: 19.09.2025. - URL: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf

2. Tillyashajxov M.N., Raximov O.A., Adilxodzhaev A.A., Dzhanklich S.M. Zabolevaemost' kolorektal'nym rakom v Uzbekistane // Taz. Xir. Onkol. – 2022. – T. 12, № 2. – S. 11-16 [Tillyashaykhov M.N., Rakhimov O.A., Adilkhodjaev A.A., Dzhanklich S.M. Incidence of colorectal cancer in Uzbekistan // Pelvic Surg. Oncol. – 2022. – Vol. 12, No. 2. – P. 11-16 (in Russ.)]. https://doi.org/10.17650/2686-9594-2022-12-2-11-16

3. Chen Y., Zhang Y., Yan Y., Han J., Zhang L., Cheng X., Lu B., Li N., Luo C., Zhou Y., Song K., Iwasaki M., Dai M., Wu D., Chen H. Global colorectal cancer screening programs and coverage rate estimation: an evidence synthesis // J. Translat. Med. – 2025. – Vol. 23. – Art. no. 811. https://doi.org/10.1186/s12967-025-06887-4

4. Cao Q., Tian Y., Deng Z., Yang F., Chen E. Epigenetic Alteration in Colorectal Cancer: Potential Diagnostic and Prognostic Implications // Int. J. Mol. Sci. – 2024. – Vol. 25 (6). – Art. no. 3358. https://doi.org/10.3390/ijms25063358

5. Pickhardt P.J., Pooler B.D., Kim D.H., Hassan C., Matkowskyj K.A., Halberg R.B. The Natural History of Colorectal Polyps: Overview of Predictive Static and Dynamic Features // Gastroenterol. Clin. North Am. – 2018. – Vol. 47 (3). – P. 515–536. https://doi.org/10.1016/j.gtc.2018.04.004

6. Liu C., Xu L., Li W., Jie M., Xue W., Yu W. Multiple biomarker-combined screening for colorectal cancer based on bisulfate conversion-free detection of fecal DNA methylation // BioMed Res. Int. – 2021. – Art. no. 1479748. https://doi.org/10.1155/2021/1479748

7. Yamashita K., Hosoda K., Nishizawa N., Katoh H., Watanabe M. Epigenetic biomarkers of promoter DNA methylation in the new era of cancer treatment // Cancer Sci. – 2018. - Vol. 109(12). – P. 3695-3706. https://doi.org/10.1111/cas.13812

8. Zhao R., Choi B.Y., Lee M.H., Bode A.M., Dong Z. Implications of genetic and epigenetic alterations of CDKN2A (p16INK4a) in

cancer // EBioMedicine. – 2016. – Vol. 8. – P. 30–39. – DOI: https://doi.org/10.1016/j.ebiom.2016.04.017

9. Fatemi N., Tierling S., Aboulkheyr Es H., Varkiani M., Nazemalhosseini Mojarad E., Asadzadeh Aghdaei H., Walter J., Totonchi M. DNA methylation biomarkers in colorectal cancer: Clinical applications for precision medicine // Int. J. Cancer. – 2022. – Vol. 151 (12). – P. 2068–2081. https://doi.org/10.1002/ijc.34186

10. Bahrami A., Hassanian S.M., Khazaei M., Gharib M., Rahmani M., Fiuji H., Jazayeri M.H., Moetamani-Ahmadi M., Ferns G.A., Avan A. The 9p21 locus as a potential therapeutic target and prognostic marker in colorectal cancer // Pharmacogenomics. – 2018. – Vol. 19 (5). – P. 463–474. https://doi.org/10.2217/pgs-2017-0096

11. Toyota M., Ahuja N., Ohe-Toyota M., Herman J.G., Baylin S.B., Issa J.P. CpG island methylator phenotype in colorectal cancer // PNAS. – 1999. – Vol. 96 (15). – P. 8681–8686. https://doi.org/10.1073/pnas.96.15.8681

12. Esteller M., Sparks A., Toyota M., Sanchez-Cespedes M., Capella G., Peinado M.A., Gonzalez S., Tarafa G., Sidransky D., Meltzer S.J., Baylin S.B., Herman J.G. Analysis of adenomatous polyposis coli promoter hypermethylation in human cancer // Cancer Res. – 2000. – Vol. 60 (16). – P. 4366–4371. https://doi.org/10.1097/00000658-199501000-00004

13. Ayub A.L.P., Perestrelo B.O., Pessoa G.C., Jasiulionis M.G. Useful methods to study epigenetic marks: DNA methylation, histone modifications, chromatin structure, and noncoding RNAs // In: Epigenetics and DNA Damage. – 2022. – P. 283–310. https://doi.org/10.1016/B978-0-323-91081-1.00012-1

14. Porcaro F., Voccola S., Cardinale G., Porcaro P., Vito P. DNA Methylation Biomarkers in Stool Samples: Enhancing Colorectal Cancer Screening Strategies // Oncol. Rev. – 2024. – Vol. 18. – Art. no. 1408529. https://doi.org/10.3389/or.2024.1408529

15. WHO Classification of Tumours Editorial Board. Digestive System Tumours. – 5th edn. – Lyon: IARC Press; 2019. – 543 p. – ISBN 978-92-832-4499-8

АҢДАТПА

CDKN2A МОЛЕКУЛАЛЫҚ-БИОЛОГИЯЛЫҚ МАРКЕРІНІҢ ТОҚ ІШЕК ОБЫРЫН ЕРТЕ ДИАГНОСТИКАЛАУДАҒЫ РӨЛІ

***М.Н. Тилляшайхов*[1], *Х.Д. Исламов*[1], *Я.В. Тен*[1], *И.П. Зияев*[1], *Я.П. Зияев*[1]**

[1]Онкология және радиология бойынша Республикалық мамандандырылған ғылыми-тәжірибелік медициналық орталық, Ташкент, Өзбекстан

Өзектілігі: *Колоректалды обыр (КРО) әлем бойынша қатерлі ісіктерден болатын өлім-жітімнің жетекші себептерінің бірі болып қала береді, бұл көбіне кеш диагностикалауға байланысты. Соңғы жылдары алдын ала ісік алдындағы өзгерістерді ерте анықтауға арналған қолжетімді әрі сезімтал молекулалық маркерлерді іздеу ерекше өзектілікке ие болды. Бұл, әсіресе ұлттық скринингтік бағдарламалары жоқ және колоноскопияның қолжетімділігі төмен мемлекеттер үшін маңызды, соның ішінде Өзбекстанда. Ең көп зерттелген маркерлердің бірі – жасуша циклін реттеуде негізгі рөл атқаратын ісік супрессоры CDKN2A генінің гиперметилденуі.*

Зерттеудің мақсаты *– тоқ және тік ішектің полиптері мен полипозы бар науқастарда CDKN2A промотор аймағының гиперметилдену жиілігін және оның дисплазияның морфологиялық белгілерімен байланысын зерттеу.*

Әдістері: *Зерттеуге ішектің ісік алды түзілімдері бар 31 науқас енгізілді. Шырышты қабық биоптаттары мен қан плазмасы метилге-спецификалық ПТР әдісімен талданды.*

Нәтижелері: *CDKN2A гиперметилденуі 17 науқаста (54,8%) анықталды. Полиптері бар науқастарда метилдену жиілігі 65%, ал полипозы бар науқастарда – 36,4% құрады (p=0,043). Морфологиялық өзгерістермен тікелей байланыс орнатылды: гиперметилденуі бар науқастарда орташа дисплазия жиі байқалды (70,6%), ал маркер теріс науқастарда жеңіл дисплазия немесе оның болмауы басым болды.*

Қорытынды: *Алынған деректер CDKN2A гиперметилденуі КРО патогенезіндегі ерте маркер болып табылатынын және ісік алды процестің үдеуімен тығыз байланысты екенін растайды. MSP-ПТР әдісі жоғары сезімталдық пен қолжетімділікті көрсетті, бұл оны Өзбекстанның өңірлік зертханаларына енгізу үшін перспективалы етеді. CDKN2A тәуекелді стратификациялау критерийі, молекулалық скринингтің компоненті және ішектің ісік алды өзгерістері бар науқастарды жекелендірілген бақылаудың негізі ретінде қолданылуы мүмкін.*

Түйінді сөздер: *колоректалды обыр (КРО), полиптер, CDKN2A, гиперметилдену, эпигенетикалық биомаркерлер, MSP-ПТР, молекулалық скрининг.*

АННОТАЦИЯ

РОЛЬ МОЛЕКУЛЯРНО-БИОЛОГИЧЕСКОГО МАРКЕРА *CDKN2A* В РАННЕЙ ДИАГНОСТИКЕ РАКА ТОЛСТОЙ КИШКИ

***М.Н. Тилляшайхов*[1], *Х.Д. Исламов*[1], *Я.В. Тен*[1], *И.П. Зияев*[1], *Я.П. Зияев*[1]**

[1]Республиканский специализированный научно-практический медицинский центр онкологии и радиологии, Ташкент, Узбекистан

Актуальность: *Колоректальный рак (КРР) остаётся одной из ведущих причин смертности от злокачественных новообразований во всём мире, что во многом обусловлено поздней диагностикой. Особую актуальность в последние годы приобретает поиск доступных и чувствительных молекулярных маркеров раннего выявления предопухолевых изменений, в том числе в странах с ограниченными ресурсами, включая Узбекистан, где отсутствуют национальные скрининговые*

программы, а доступность колоноскопии остаётся низкой. Одним из наиболее изученных является гиперметилирование гена-супрессора опухолей CDKN2A, играющего ключевую роль в регуляции клеточного цикла.

***Цель исследования** – изучение частоты гиперметилирования промоторной области CDKN2A у пациентов с полипами и полипозом толстой и прямой кишки, а также его ассоциации с морфологическими признаками дисплазии.*

***Методы:** В исследование включён 31 пациент с предопухолевыми образованиями кишечника. Биоптаты слизистой и плазма крови были проанализированы методом метил-специфической ПЦР.*

***Результаты:** Гиперметилирование CDKN2A выявлено у 17 пациентов (54,8%). При полипах частота метилирования составила 65%, при полипозе – 36,4% (p=0,043). Установлена прямая связь с морфологическими изменениями: у пациентов с гиперметилированием чаще наблюдалась умеренная дисплазия (70,6%), тогда как при отрицательном статусе по маркеру преобладали лёгкая дисплазия или её отсутствие.*

***Заключение:** Полученные данные подтверждают, что гиперметилирование CDKN2A является ранним маркером в патогенезе КРР, тесно связанным с прогрессией предопухолевого процесса. Метод MSP-PCR показал высокую чувствительность и доступность, что делает его перспективным для внедрения в региональные лаборатории Узбекистана. CDKN2A может быть использован как критерий стратификации риска, компонент молекулярного скрининга и основа для персонализированного наблюдения за пациентами с предопухолевыми изменениями кишечника.*

***Ключевые слова:** колоректальный рак (КРР), полипы, CDKN2A, гиперметилирование, эпигенетические биомаркеры, MSP-PCR, молекулярный скрининг.*

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Information about the Authors:
M.N. Tillyashaykhov – Doctor of Medical Sciences, Professor, Director of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan, tel.: +998712460513, e-mail: info@cancercenter.uz, ORCID: 0000-0001-6428-9550;
Kh.D. Islamov – Candidate of Medical Sciences, Head of the Coloproctology Department, Republi-can Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan, tel.: +998979008557, e-mail: dr.hurshid@mail.ru, ORCID: 0000-0002-9970-1936;
Ya.V. Ten – Manager of the Coloproctology Department, Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan, tel.: +998979008557, e-mail: Tenksiy06@mail.ru, ORCID: 0000-0002-9970-1936;
I.P. Ziyaev – General Oncologist, Department of Comprehensive Diagnostics and Treatment of Patients, Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan, tel.: +998937849777, e-mail: palitdinovich@gmail.com, ORCID: 0009-0008-6203-6136;
Ya.P. Ziyaev – General Oncologist, Department of Comprehensive Diagnostics and Treatment of Patients, Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Tashkent, Uzbekistan, tel.: +998934430080, e-mail: palitdinovich@gmail.com, ORCID: 0009-0009-2905-8859;

***Address for Correspondence:** Ya.V. Ten, Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology, Farobi St. 83, Shaykhantaur district, Tashkent 100179, Uzbekistan.*